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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/259,658	Applicant(s) Colyer
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 17, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-18, 20, and 21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-18, 20, and 21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim 21 has been added.

Claim 19 was previously canceled.

Claims 1, 8,14, and 17 have been amended.

Claims 1-18 and 20-21 are pending and under consideration.

Continued Prosecution Application

1. The request filed on May 17, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/259,658 is acceptable and a CPA has been established. An action on the CPA follows.

Rejections Withdrawn

2. Claims 8 and 14 rejected under 35 U.S.C. 112, second paragraph, in light of the amendment of the claims to provide antecedent basis for terms recited and the covalent modification has been clarified.

3. Claim 1 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the amendment of the claims to positively recite limitations directed to covalent modification and the sample being added to both the first polypeptide and the binding partner.

4. Claims 1-5, 8, 12-14, 16, 18 rejected under 35 U.S.C. 102(e) as being anticipated by Bronstein (US Pat. 5,849,495), in light of the amendment of the claims to recite the term enzyme covalent modification.

5. Claims 1-7,14-15 rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al (5,439,797), in light of the amendment of claim 1 to measure a covalent modification.

6. Claims 1-7,14 rejected under 35 U.S.C. 102(b) as being anticipated by Lakowicz et al (US Pat. 5,631,169) in light of the amendment of claim 1 to measure a covalent modification.

7. Claims 1-6,10-14, 18 rejected under 35 U.S.C. 102(e) as being anticipated by Gallatin (US Pat 5,989,843 or. 5,837,822)in light of the amendment of claim 1 to measure a covalent modification.

8. Claims 1 and 9 rejected under 35 U.S.C. 102(b) as being anticipated by Sehr (US Pat. 5,341,215)in light of the amendment of claim 1 to measure a covalent modification.

Rejections Maintained

9. Claim 17 rejected under 35 U.S.C. 102(e) as being anticipated by Mills (US Pat. 5,773,592) for reasons of record in papers number 10, 12 and response to arguments below.

10. Claims 1-2, 14, 16, 18 and 20 rejected under 35 U.S.C. 102(b) as being anticipated by Avruch et al (US Pat. 5,582,995), as previously applied to claims 1 and 20, for reasons of record in paper number 12, paragraph 31.

11. Claims 1-2, 10-11 and 20 rejected under 35 U.S.C. 102(e) as being anticipated by Josiah et al (6,146,842), as previously applied to claims 1 and 20, for reasons of record in paper number 12, paragraph 32.

Please Note: The examiner is reading the phrase "and covalent modification of at least one of the polypeptides results in modulation of association and is required for said association" as a conditional phrase, which may or may not take place because the first polypeptide and the binding partner are not defined to covalently modify each other and no other reagent that would covalently modify their binding is added to the assay method.

Response to Arguments

12. The rejection of claim 17 under 35 U.S.C. 102(e) as being anticipated by Mills (US Pat. 5,773,592) is asserted to "not teach a polypeptide pair comprising a first polypeptide immobilized on a support and a second polypeptide bound to the first polypeptide, wherein the binding of the polypeptides is detectable and covalent modification of at least one of the polypeptides results in modulation of the binding, and concludes that the binding of an enzyme to a substrate is via a weak, non-covalent bond.

13. It is the position of the examiner that Mills et al (US Pat. 5,773,592) discloses a composition of "a polypeptide pair comprising a first polypeptide immobilized to a support and a second polypeptide bound to the first polypeptide", wherein the first and second polypeptides of Mills are bound to each other through a biocompatible polymer.

It is the position of the examiner that Mills et al disclose a broad class of pharmaceutical agents referred to as luminide agents that upon covalent modification are detectable.

The "luminide agents are three part or four part molecules where each part is a functionality with a defined purpose. Exemplary Luminides are A-B-C , D-A-B-C, A-D-B-C, wherein A represents a functionality which is activatable by the environment and capable of transferring energy from its own excited state to the B functionality which is an energy acceptor. Upon receiving energy from A, B achieves an excited state which relaxes through the heterolytic cleavage of the covalent bond of B with C where C is a drug moiety which is released into the intracellular compartment where activation of A occurred. Released C can act locally or at a distant site. D serves as an electron transfer functionality which gains (loses) electrons from (to) the environment and donates (accepts) electrons to (from) A to activate it so that the energy of excited A is transferred to B with release of C as occurs for the three functionality case."

Additional "drugs which are not inherently photo chromic bleaches in that they lack a nucleophilic group which will form a reversible covalent bond with the B functionality can be derivatized with a known bleaching nucleophilic group such as cinnamate, sulfite,

phosphate, carboxylate, thiol, or amine group to transform them into bleaching agents of the B functionality such as a cationic dye". See Table 3 below for the structure of a exemplary drug molecules.

Clearly Mills et al discloses an immobilized polypeptide pair, wherein covalent modification of one of the polypeptides results in modulation of association, and results in a detectable signal. The reference anticipates the instantly claimed invention.

14. The rejection of claims 1-2, 14, 16, 18 and 20, as previously applied to claims 1 and 20 under 35 U.S.C. 102(b) as being anticipated by Avruch et al (US Pat. 5,582,995) is asserted not to anticipate the claimed invention by "submitting that Avruch et al do not teach a polypeptide pair wherein covalent modification of at least one of the polypeptides results in modulation of association of the polypeptides of the pair."

15. It is the position of the examiner that Avruch et al does disclose teach a polypeptide pair wherein covalent modification of at least one of the polypeptides results in modulation of association of the polypeptides of the pair, wherein a polypeptide pair is disclosed, one being a transferase which covalently modifies a polypeptide substrate that is immobilized, and covalent modification of the immobilized substrate results in modulation of the transferase enzyme/polypeptide substrate association, specifically dissociation from the substrate. The covalent modification of the polypeptide substrate results in an association that is specific between the polypeptide and the enzyme and a farnesyl residue, wherein the

covalent addition of a farnesyl residue modulates the association of the enzyme and the farnesyl residue containing substrate (see col. 7, lines 7-27 and col. 8, lines 28-29).

The covalent modification of one of the polypeptides (col. 6, lines 1-47) is assayed through measuring the remaining GTPase activity from the 32P-GTP remaining bound to c-rasH (see col. 8, lines 50-54) or by immunoblotting with a Ras specific antibody with a chemiluminescent label (see col. 8, lines 27-29).

(Instant claim 18) The method of Avruch et al also evaluates the effect of a modulator (see col. 13, lines 25-67 and col. 14, lines 1-36), wherein comparison of the binding of polypeptide pairs was carried out to evaluate the binding in the presence of a candidate modulator (see col. 6, lines 14-67, col. 7, lines 1-7 and col. 8, lines 40-67 and col. 9, lines 1-27).

16/

16. The rejection of claims 1-2, 10-11 and 20 rejected under 35 U.S.C. 102(e) as being anticipated by Josiah et al (6,146,842) is argued through asserting that Josiah et al do not teach that a covalent modification of at least one of the polypeptides results in modulation of association and is required for said association.

17. It is the position of the examiner that upon binding of the enzyme to the substrate and the covalent addition of either farnesyl or prenyl group to the substrate, the binding of the enzyme to the substrate is modulated such that the enzyme will dissociate from the modified substrate. The covalently modified substrate would evidence the presence of a detectable label due to the covalent addition of the farnesyl or prenyl group to immobilized first polypeptide. The detectable label permits the assaying of the modification of the

immobilized substrate due to the association of the binding partner (enzyme) and the immobilized first polypeptide substrate. The association is required for the covalent modification of the immobilized first polypeptide and is also required for the addition of a detectable label to the immobilized substrate so that the covalent modification can be assayed through the presence of a label associated with the covalently added group.

The recitation of the phrase "second polypeptide" is being read to refer to the "binding partner polypeptide", as no other specific function, structure or interaction is defined.

Josiah et al teaches the utilization of radio labeled molecules which are measured in a micro plate scintillation and luminescence counter, a type of scintillation proximity assay (see col. 5, lines 46-62; col. 7, lines 12-27).

The reference anticipates the instantly claimed invention.

New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 112

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 1-18, 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to recite the word "enzyme", but none of the methods steps detect the presence of the enzyme in the sample defined in the preamble of the claim. The methods steps do not correlate with the newly amended preamble. How is the enzyme detected in the sample is the modification is assayed? Is the second polypeptide or the sample the enzyme, or is the enzyme the specific binding partner? Clarification is requested.

Claim 1 recites the phrase in subsection c) "the immobilized polypeptide with the second polypeptide". In light of no second polypeptide having been provided, what is the second polypeptide? Is the second polypeptide the binding partner? The claim does not provide antecedent basis for the phrase "second polypeptide" prior to subsection c). Clarification of what the second polypeptide is, is requested.

Claim 1, subsection d) recites the phrase "contacting said immobilized polypeptide and said binding partner polypeptide with said sample". How do the second polypeptide recited in subsection c) differ from the binding partner polypeptide of subsection d)? How are the first and second polypeptides related or not related to one another. What function, biological activity or binding relationship do the second polypeptide, the first polypeptide, the binding partner, the enzyme of the preamble and the modification that is assayed have to one another? How is the modification indicative of the enzyme that covalently modifies a polypeptide in a sample, if the enzyme modifies the second polypeptide that is not immobilized and the binding partner that is capable of binding the immobilized first polypeptide does not bind the immobilized polypeptide in light of the enzyme in the sample binding the second polypeptide rather than the first polypeptide which has not been modified? What is assayed if no modification takes place and no association

of the binding partner and the first polypeptide takes place? Is the second polypeptide the same polypeptide as the immobilized first polypeptide? Clarification of the binding relationships of the first and second polypeptides, the enzyme, and the binding partner is requested.

Claim 1 in subsection e) recites the phrase "assaying the modification of at least one of the polypeptides". What causes the modification of one of the polypeptide ? How does the modification take place? The binding partner need only be capable of association with the first polypeptide, what caused the association to become potentiated? Clarification of what modifies the first polypeptide is requested.

Claim 13 add an "agent" that is capable of covalently modifying one or both of said polypeptides". What is the "agent" if it is not the enzyme that can covalently modify a polypeptide? Does the method comprise two enzymes? If the "agent" of claim 13 is biologically and functionally different from the enzyme being detected in claim 1, is the agent what covalently modifies the immobilized polypeptide? If the agent is what covalently modifies the polypeptide, is it not required to be present in the method of claim 1? How many different defined reagent are present in the assay method of claim 13 which depends from claim 1; first and second polypeptides, a binding partner, an enzyme and an agent? How is the covalent modification of the second polypeptide determined in light of the binding partner being specific for the first polypeptide? Clarification of what the agent is, relative to the newly amended preamble of claim 1 that detects an enzyme is requested.

Claim 15 recites the phrase "measured in real time". What amount of time the assay is measured in is not distinctly claimed. How does real time differ from time? Clarification is requested.

Claim 17 on lines 5-6 recites the phrase "said binding partner polypeptide". This phrase lacks antecedent basis in the claim which recites first and second polypeptides bound to each other, but neither of the first and second polypeptides are defined to be the binding partner of the other polypeptide. One polypeptide can be bound to a second polypeptide through a linker or a specific binding relationship. The type of binding is broadly recited through the recitation of the word "bound". An additional embodiment is disclosed to comprise a plurality of polypeptides that contain a number of cleavage sites for endopeptideases and binding of the binding partner only takes place upon the polypeptide being cleavage (see col. 8, lines 21-38). Clarification of the members of the polypeptide pair is requested relative to the phrase that lacks antecedent basis in the claim.

Claim 17 recites the phrase "is required for said association". This phrase refers back to both the phrase "covalent modification" and "results in modulation"; which of these two phrases the phrase "is required for said association" refers is unclear. The association could require a covalent binding of the two polypeptides which would modulate the binding to be one that comprises a strong covalent bond. The association of the bound polypeptides may also be one that is the result of an external source which changes the structural conformation of one of the two polypeptides resulting in modulation of association. As no external modulating component is required in the complex of claim 17, to which functional part of the sentence does the phrase "is

required for said association" refer ? What type of binding is modulated? Clarification is requested.

Claim 17 recites the phrase "the binding of the polypeptides is detectable". What does the binding if the polypeptides that are already bound to one another? What binds to the polypeptides and is detectable? What is detectable, the polypeptide pair or what binds to the polypeptide pair? How can a pair of polypeptides comprise a third polypeptide that is detectable and be considered a pair? Clarification is requested.

Claim 21 provides first and second polypeptides and a test sample, but they are not combined. How can the association of the first and second polypeptide take place if they are not in proximity to one another ? As no modifying enzyme was provided as a control sample, how can the association of the first and second polypeptides be compared with a control sample for the modifying enzyme?

Claim Rejections - 35 U.S.C. § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

21. Claims 1-3, 5, 10, 12-17 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Shone et al (US Pat. 5,962,637; filing date December 3, 1996).

The claimed invention is directed to a method of detecting the presence of a modifying enzyme in sample, wherein the enzyme modifies a polypeptide covalently. The method comprises the steps of :

providing a polypeptide pair, a first polypeptide and a binding partner;

immobilizing the first polypeptide to a physical support;

contacting the immobilized polypeptide with the second polypeptide;

contacting the immobilized polypeptide with said binding partner polypeptide

assaying the modification of at least one of the polypeptides by measuring the association of the binding partner polypeptide to the first polypeptide.

Shone et al disclose a method of detecting the presence of a modifying enzyme in sample, wherein the enzyme modifies a polypeptide covalently, and the enzyme is botulism or tetanus toxin. The method comprises the steps of :

providing a polypeptide pair, a first polypeptide and a binding partner (see Shone et al, claim 1, first polypeptide is a substrate polypeptide and the binding partner is an antibody capable

of binding the substrate after covalent modification with the enzyme and is labeled with an enzyme);

immobilizing the first polypeptide to a physical support (see Shone et al claim 1, attached to solid support, the immobilized polypeptide is labeled with the detectably labeled antibody to form a detectable complex upon covalent modification with the enzyme in a sample);

contacting the immobilized polypeptide with the second polypeptide (test compound, see Shone et al claims 1, 2 and 9);

contacting the immobilized polypeptide with said binding partner polypeptide (see claims 1 and 9, Shone et al)

assaying the modification (cleavage of substrate) of at least one of the polypeptides by measuring the association of the binding partner polypeptide (antibody binds, see Shone et al claim 1) to the first polypeptide (see Shone et al, claims 6-7, detection of label) .

(Instant claim 5 and 10) An antibody linked to an enzyme is also taught to include a radioactive label (see Shone et al col. 6, lines 37-39) or a fluorescent label (see Shone et al, col. 6, lines 39-42).

(Instant claims 12-13) The antibody was modified by linking an enzyme to the antibody (see Shone claim 6), or an antibody that binds to the binding partner antibody that is linked to an enzyme (see Shone et al , claim 10).

(Instant claim 13) The assay also comprises the addition of a protease to the test compound which is capable of functioning as an agent (see Shone et al, claim 9), an enzyme that can covalently modify a polypeptide, such as activate an inactive endopeptidase.

(Instant claim 17) An additional embodiment disclosed is a polypeptide pair comprising a first polypeptide immobilized to a support and a second polypeptide bound to the first polypeptide, wherein the two polypeptides are an endopeptidase peptide substrate linked to a carrier protein that is maleimide activated BSA, which is bound to a microtiter plate (see Shone et al col. 15, lines 45-50). The binding of the two polypeptide one to the other is detectable, and a covalent modification of one of the polypeptides is required for the association of the first polypeptide endopeptidase substrate with the binding partner polypeptide.

The assay is carried out over time, thus defining an assay carried out in real time.

The reference anticipates the instantly claimed invention.

22. Claims 1-7, 12-18, 20-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Bronstein et al (US Pat. 6,243,980).

Bronstein et al (US Pat. 6,243,980) discloses the claimed invention directed to a method of detecting the presence of a modifying enzyme in sample, wherein the enzyme modifies a polypeptide covalently (see col. 5, lines 53-57; col. 8, lines 36-67 through col. 9, lines 1-8 and col. 10, lines 1-25). The method comprises the steps of :

providing a polypeptide pair, a first polypeptide and a binding partner (see Bronstein Figures 2a-2b and 5a-5; a first polypeptide that is labeled and comprises a cleavage site for an

enzyme and an antibody (binding partner) that is labeled and specific for a component of the first polypeptide);

immobilizing the first polypeptide to a physical support, which is detectable (see Figures 2a-2b and col. 2, lines 1-50; col. 5, lines 43-52);

contacting the immobilized polypeptide with the second polypeptide (test sample containing enzyme which is a polypeptide; see claims 12-14);

contacting the immobilized polypeptide with said binding partner polypeptide (labeled antibody, see claim 6-11)

assaying the modification of at least one of the polypeptides by measuring the association of the binding partner polypeptide to the first polypeptide (see claim 1, subparagraph (e).

The reference teaches the utilization of positive control tubes (see col. 4, line 40) the comparison of reaction products based upon the presence or absence of the second polypeptide in a sample (see col. 3, lines 14-30, Figure 5(a&b), as well as comparison of test samples with background signals and positive test-responsive signals (see col. 6, lines 28-40).

The detectable labels on the immobilized first polypeptide and the binding partner are different from each other, specifically fluorescein (first polypeptide, see col. 5, line 47; col. 7, line 58 and line 60) and alkaline phosphatase (binding partner, col. 5, line 67; col. 7, lines 8-28).

The detectable signal is generated by an energy transfer or energy quenching between the two labels (see col. 7, lines 37-67 and col. 8, lines 1-11).

The assay is carried out with a linear detection window in less than 5 minutes; the assay is carried out in real time (see col. 10, lines 10-11).

The reference anticipates the instantly claimed invention.

23. Claim 17 is rejected under 35 U.S.C. 102(e) as being anticipated by Kilburn et al (US Pat. 5,962,289).

Kilburn et al disclose the claimed invention directed to a polypeptide pair, the pair comprising a first polypeptide immobilized on a support (see Kilburn claims 3, 5-7; claims 18-120) and the second polypeptide being bound to the first polypeptide (bound through cleavage site, see Kilburn claim 2), wherein the polypeptide pair is detectable (see claim Kilburn, claims 11-12).

The covalent modification of at least one of the polypeptides results in modulation of the binding, wherein the modification is insertion of a cleavage site (see Kilburn claim 2) which is required for the association of the first and second polypeptides (see Kilburn, claim 1, hybrid protein), but upon cleavage of the site would result in the modulation of the association of the first and second polypeptides (the polypeptides would no longer be associated). One of the two polypeptides is a binding partner used for a immobilizing the polypeptide pair on the support (see Kilburn, claims 1-4). The reference anticipates the instantly claimed invention.

Claim Rejections - 35 U.S.C. § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. Claims 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shone et al as applied to claims 1-3, 5, 10, 12-17 and 20 above, in view of Taremi et al (US Pat. 5,981,167).

See discussion of Shone et al above. The reference teaches a method of detecting an endopeptidase in a sample, specifically botulinum toxin, wherein the detecting utilizes an immobilized polypeptide assays the covalently modified of one of the polypeptides as a measurement of the association of the enzyme and the immobilized polypeptide, and teaches the utilization of a radioactive detectable label.

The reference assays for the presence of the modification but differs from the instantly claimed invention by failing to show the assay method to monitor changes in the molecular mass of the immobilized polypeptide based upon changes in modified polypeptides.

Taremi et al teach the a method that measures the covalent modification of an immobilized polypeptide with an enzyme protease (see figures 8a,8b,9a and 9b) in an analogous art for the purpose of determining the cleavage of a substrate due to the presence of an enzyme in a sample, and shows the measurements taken based on changes in molecular mass(see col. 1, lines 35-46;

col. 2, lines 30-32; col. 2, lines 42-58), the advantage being not having to utilize a radioactive label (see col. 1, line 30-31), the labeling process does not inactivate the substrate (see col. 1, lines 27-28) and provides an assay format for high-throughput analysis of samples (see col.1, line 30).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the assaying method of Shone et al to include the assaying method of Taremi et al because the method of Taremi has the advantage of measuring modifications of immobilized polypeptides with utilizing a radioactive label (see col. 1, line 30-31), the labeling process does not inactivate the substrate (see col. 1, lines 27-28) and provides an assay format for high-throughput analysis of samples (see col.1, line 30)..

The person of ordinary skill in the art at the time the invention was made would have been motivated by the reasonable expectation of success of assaying the modification of at least one polypeptide through changes in the molecular mass in view of the guidance and teaching of Taremi because Taremi et al teach that mass spectrometry provides an accurate measurement of molecular mass and the assay is "readily adaptable to any enzyme-substrate reaction (see col. 2, lines 36-37)."

Shone et al in view of Taremi obviate the instantly claimed invention.

Claims 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shone et al as applied to claims 1-3, 5, 10, 12-17 and 20 above, in view of Little et al (US Pat. 6,322,970).

See discussion of Shone et al above. The reference teaches a method of detecting an endopeptidase in a sample, specifically botulinum toxin, wherein the detecting utilizes an immobilized polypeptide assays the covalently modified of one of the polypeptides as a measurement of the association of the enzyme and the immobilized polypeptide, and teaches the utilization of a radioactive detectable label.

The reference assays for the presence of the modification but differs from the instantly claimed invention by failing to show the assay method to monitor changes in the molecular mass of the immobilized polypeptide based upon changes in modified polypeptides.

Little et al teach the a method that measures the covalent modification of an immobilized polypeptide with an endopeptidase (see claims 60-65 and 66-79; also see claims 59, 92-95 and) in an analogous art for the purpose of showing the measurements taken based on changes in molecular mass(see claims 59, and 92-95), the advantage being not having to utilize a radioactive label (see col. 4, line 11).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the assaying method of Shone et al to include the assaying method of Little because the method of Little has the advantage of measuring modifications of immobilized polypeptides without the use of a radioactive label.

The person of ordinary skill in the art at the time the invention was made would have been motivated by the reasonable expectation of success of assaying the modification of at least one polypeptide through changes in the molecular mass in view of the guidance and teaching of Little because Little et al teach that mass spectrometry provides an accurate measurement of molecular

mass (weight) for relatively short polypeptides, especially immobilized polypeptides that comprise a cleavable linker (see Little et al, col. 3, lines 28-41; col. 3, lines 66-67, col. 4, lines 1-14; col. 4, lines 38-46 and claims).

Shone et al in view of Little obviate the instantly claimed invention.

Conclusion

26. This is a non-final action.

27. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

28. Faff (US Pat. 6,268,123) is cited to show a method of detecting a viral enzyme in a sample utilizing an immobilized polypeptide substrate (a binding partner; see claims 2-7).

29. Harley et al (US Pat. 5,863,726) is cited to show a method of determining telomerase activity.

30. Mann et al (US Pat. 6,242,173) is cited to show an immunoassay for the determination of serine proteases.

31. Schmidt et al (US Pat. 5,965,699) is cited to show an assay for the determination of Clostridium botulinum serotype A proteolytic activity in a sample (see all claims).

32.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
July 3, 2002

MARK NAVARRO
PRIMARY EXAMINER